

A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model

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Background: Oral azelastine, a nonsteroidal antiinflammatory respiratory investigational drug has demonstrated activity in the treatment of allergic rhinitis and asthma with a good safety profile.

Methods: Azelastine nasal spray was compared with sustained-release oral chlorpheniramine maleate and placebo for efficacy and safety in the treatment of seasonal allergic rhinitis in a double-dummy, two-center, 2-day, double-blind, randomized, dose-ranging, parallel-groups, onset and duration of action study. Two hundred sixty-four subjects reported to an outdoor park on Saturday morning during the height of the fall pollen season and remained there for 8 hours that day and the next to ensure maximal exposure to seasonal aeroallergens. Symptom diary cards were collected hourly Saturday from 8:00 AM to 10:00 AM (baseline period). Subjects who had sufficient symptoms were randomized into five groups and received medication at 10:00 AM and 10:00 PM on Saturday and at 10:00 AM on Sunday: azelastine 0.1% (1 spray [0.12 mg] per nostril every 12 hours, 2 sprays per nostril every 12 hours, or 2 sprays per nostril once daily), Chlor-Trimeton Repetabs (12 mg twice daily), or placebo (twice daily). Diary cards were completed hourly (11:00 AM to 4:00 PM) and at 6:00, 8:00, and 10:00 PM on Saturday and again hourly on Sunday (from 8:00 AM to 4:00 PM) to evaluate rhinitis symptoms and adverse events.

Results: Two hundred fifty-nine subjects completed the study. The groups that received 2 sprays of azelastine per nostril once and twice daily and the chlorpheniramine group had statistically significantly more improvement in total rhinitis symptoms than the placebo group without serious adverse events.

Conclusions: This study supports a once to twice daily dosing regimen for 2 sprays of 0.1% azelastine in the acute treatment of allergic rhinitis with onset of action within 2 to 3 hours. (*J ALLERGY CLIN IMMUNOL* 1994;94:972-80.)

Key words: Azelastine, allergic rhinitis, chlorpheniramine

Azelastine, a nonsteroidal antiinflammatory respiratory investigational drug, when given orally, has demonstrated activity and safety in the treatment

Abbreviations used

ANOVA: Analysis of variance

MSC: Major symptom complex

TSC: Total symptom complex

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of rhinitis and asthma.¹⁻⁵ Azelastine has a broad spectrum of antiallergy and antiinflammatory pharmacologic activities in both upper and lower airways, as demonstrated in human and animal model systems.⁶ Azelastine prevents activation of basophils, mast cells, eosinophils, macrophages, and monocytes⁷⁻¹⁰ and blocks the synthesis, release, or target receptors of several mediators of the im-

mediate inflammatory response, including histamine, platelet activating factor, and acetylcholine.¹¹⁻¹³ Azelastine may also regulate late-phase allergic responses by inhibiting leukotriene-mediated and T cell-dependent responses¹⁴ and by preventing the downregulation of β_2 -receptors.¹⁵

This study was designed to examine the efficacy, safety, and onset and duration of action of topical azelastine in the treatment of seasonal allergic rhinitis, a disease that continues to afflict about 15% of the population in the United States and to be a major cause of lost school and work days.¹⁶ We compared three doses of azelastine and one dose of sustained-release chlorpheniramine maleate with placebo in a double-dummy, two-center, 2-day, double-blind, randomized, dose-ranging, parallel-groups, onset and duration of action study. The criteria to examine medication efficacy were: (1) improvement in total or major symptom diary scores, which were the primary efficacy measurements; (2) improvement in individual symptom diary scores; and (3) subject global evaluations. Safety was assessed by means of laboratory evaluations, physical examinations, and monitoring adverse drug experiences.

METHODS

Study design overview

The study design was developed by Connell¹⁷ and modified by Weiler et al.¹⁸ The objectives were to examine efficacy, safety, and onset and duration of action of three doses of azelastine nasal spray and orally administered sustained-release chlorpheniramine as compared with placebo in the treatment of seasonal allergic rhinitis. Approval to conduct the study was obtained from each investigator's local institutional review board. All subjects signed a certification of informed consent before participation.

Entry criteria

To be considered for enrollment, subjects were required to: (1) have a history of fall seasonal allergic rhinitis for at least the 2 previous seasons; (2) demonstrate a positive response (wheal ≥ 3 mm larger than the negative control) by prick or puncture skin testing to a prevalent allergen in season at the time of the study; (3) be between the ages of 12 and 65; (4) have no evidence of any significant medical abnormalities; and (5) have screening laboratory test values (hematology, serum chemistry, and urinalysis) within the normal range or clinically not abnormal. Women could not be pregnant or nursing an infant; and, if sexually active and of childbearing potential, they had to use acceptable methods of contraception and to have a negative pregnancy test result. Subjects were excluded if they

had: (1) a clinically significant nasal anatomic deformity; (2) an episode of sinusitis within 2 months of study entry; or (3) a history of asthma, unless the subject had received no regularly administered anti-asthma medication for at least 24 consecutive months before entering the study. Rescue medications and other drugs with antiallergy activity were prohibited for appropriate intervals before and during the study.

Symptom scores and adverse events

Subjects were asked to rate symptoms (as described in Table 1) and to indicate adverse events on the diary card. Subjects also provided global evaluations at the end of the study.

Protocol

Subjects who successfully met all screening criteria were instructed to appear at the park site for day 1 of the study on Saturday (August 16, 1989 for the Iowa City site and October 7, 1989 for the San Diego site) at 7:30 AM. On arrival at the park, subjects were questioned about use of concomitant medications and the occurrence of adverse experiences since the screening visit and were evaluated to determine whether they continued to meet the inclusion criteria. Each subject then completed a diary card at 8:00, 9:00, and 10:00 AM (cards 1 to 3).

Symptom diary cards were scanned each hour by a card reader into an IBM-compatible computer with SymptomCardReader software (CompleWare Corporation, Iowa City, Iowa). Cards were examined by the computer to determine whether entries were missing or inappropriate, and cards needing correction were immediately returned to the subjects for clarification. The SymptomCardReader program was used after entry of the 10:00 AM card to determine whether or not subjects met the minimum aggregate total symptom complex (TSC) severity score of 12 on cards 1 to 3.

At 10:00 AM qualified subjects were randomized to double-blind treatment and received the first dose of medication. They remained in the park, completing diary cards hourly, until 4:00 PM. Subjects went home and completed three additional diary cards at 6:00, 8:00, and 10:00 PM and took a second dose of medication at 10:00 PM.

Subjects returned to the park on Sunday at 7:30 AM with the three completed evening diary cards and were again questioned regarding concomitant medication use and adverse experiences. They resumed scoring symptoms hourly from 8:00 AM until 4:00 PM. The third and final dose of medication was given after the 10:00 AM Sunday diary card was completed. At 4:00 PM on Sunday, subjects provided a global rating of the effectiveness of the medication. A follow-up evaluation was completed within 7 days of the park portion of the study, which included a physical examination, repeat laboratory tests, review of concomitant medication use, and documentation of adverse drug reactions.

TABLE 1. Symptom scoring scales**I. Stuffiness**

Symptoms evaluated: stuffy left nostril and stuffy right nostril

Definitions and values

- 0: Clear — fully open, no obstruction of air passage
- 1: Slightly blocked — barely noticeable blockage of air passage
- 2: Stuffy — noticeable partial blockage but not bothersome
- 3: Very stuffy — noticeable partial blockage and bothersome
- 4: Blocked — cannot move any air through nostril

II. Nose blows and sneezes

Symptoms evaluated: nose blows in the last hour and sneezes in the last hour

Definitions and values

Actual number from 0 to 5

6: 6 to 9

7: 10 to 15

8: More than 15

III. Other symptoms

Symptoms evaluated: itchy nose right, itchy nose left, runny nose right, runny nose left, sniffles, postnasal drip, dry nose, watery eyes, itchy eyes/ears, itchy throat, cough

Definitions and values

0: None — no symptoms whatsoever

1: A little — very mild symptoms, barely noticeable, do not interfere with activity

2: Moderate — mild symptoms, noticeable but do not interfere with any activity

3: Quite a bit — bothersome symptoms, which very slightly interfere with activity

4: Severe — bothersome symptoms, which interfere modestly with activity

5: Very severe — very bothersome and disabling symptoms

IV. Subject global evaluation scale

+3 = very much better; +2 = much better; +1 = a little better

0 = no change

-1 = a little worse; -2 = much worse; -3 = very much worse

MSC = the sum of the scores for runny nose right, runny nose left, itchy nose right, itchy nose left, sniffles, nose blows, sneezes, and watery eyes.

TSC = the sum of the scores for runny nose right, runny nose left, itchy nose right, itchy nose left, sniffles, nose blows, sneezes, watery eyes, itchy eyes/ears, itchy throat, dry nose, cough, and postnasal drip.

Medication regimens

Subjects were randomized to one of five groups with a balanced block design: 10 subjects in each block were equally divided among the five groups. Azelastine nasal spray used in this study was 0.1%, and 1 spray delivered 0.12 ml (0.12 mg) of azelastine hydrochloride. Group 1 received 1 spray of azelastine in each nostril every 12 hours (0.48 mg daily); group 2 received 2 sprays of azelastine in each nostril in the morning on both Saturday and Sunday (0.48 mg daily); group 3 received 2 sprays of azelastine in each nostril every 12 hours (0.96 mg daily); group 4 received Chlor-Trimeton Repetabs 12 mg every 12 hours; and group 5 received placebo (2 sprays in each nostril every 12 hours). Bottles containing placebo spray and placebo tablets were matched with active medication for blinding in this double-dummy design.

Statistical evaluation of efficacy

Evaluation periods were: *baseline period*—cards 1 to 3 (2, 1, and 0 hours before medication); *period 1*—cards 4 to 9 (1 to 6 hours after the first dose of medication);

period 2—cards 10 to 12 (at home 8 to 12 hours after the first dose of medication); *period 3*—cards 13 to 15 (10 to 12 hours after the second dose of medication); and *period 4*—cards 16 to 21 (1 to 6 hours after the third dose of medication).

Baseline TSC and major symptom complex (MSC) severity scores were compared among treatment groups with a two-factor analysis of variance (ANOVA); factors examined treatment groups, investigators, and treatment-by-investigator interaction. The average of the values recorded on the first three cards (pretreatment scores) was used as the baseline for each subject. The primary efficacy measurement was the mean percent or absolute mean change from baseline for the TSC or MSC severity scores for each evaluation period when all available data were used. An overall intent-to-treat analysis was done on the basis of each subject's average of all responses during treatment, as well as an end-point analysis on the basis of the last observation for each subject during treatment by using ANOVA. Comparisons of each active treatment with placebo were assessed by *t* tests with the mean square error

TABLE II. Baseline values for TSC and MSC scores

Group	Number/group	TSC (SEM)	MSC (SEM)	Mean age (yr)	Sex	
					M	F
1 — Azelastine 1 every 12 hours	54	15.94 (0.93)	10.27 (0.67)	27.1	21	33
2 — Azelastine 2 daily	54	16.30 (0.91)	10.35 (0.65)	28.4	30	24
3 — Azelastine 2 every 12 hours	54	15.42 (0.85)	9.66 (0.62)	27.9	25	29
4 — Chlorpheniramine	52	15.54 (1.01)	9.83 (0.67)	24.8	22	30
5 — Placebo	50	16.23 (0.96)	9.73 (0.67)	25.5	30	20

SEM, Standard error of the mean.

from the ANOVA. A supplementary analysis was performed by ANOVA for the subset of subjects that completed double-blind treatment with regard to changes in the primary efficacy measurements. Secondary efficacy measurements consisted of mean percent and absolute mean change in individual symptom scores and in TSC plus stuffiness and MSC plus stuffiness, which were analyzed in a similar manner. Finally, treatment differences for global evaluations, done by the subjects, were analyzed by the Cochran-Mantel-Haenszel test, controlling for investigators. The subject scores at each of the 18 assessment time points during treatment were analyzed (with the same two-way ANOVA) by comparing mean percent change from baseline in TSC and MSC severity scores between placebo and each active treatment.

The level of significance for all tests was $p \leq 0.05$. Clinically significant improvement was defined as at least a twofold increase in mean improvement after active treatment over that achieved by placebo. All pairwise treatment comparisons used two-tailed tests. Statistical analyses were performed with SAS software (Release 6.03; SAS Institute, Cary, N.C.) on a Hewlett-Packard computer series 9000, model 370 running HP-UX version 6.5 (Hewlett-Packard, Palo Alto, Calif.).

Evaluation of safety

Adverse experiences, laboratory parameters (hematology studies, serum chemistry and electrolyte measurements, and urinalysis), vital signs, body weights, and physical examinations were evaluated for all subjects randomized to double-blind treatment. Treatment-emergent adverse experiences (those reported during double-blind treatment, which did not occur or were less severe during baseline) were summarized by treatment. The proportion of subjects with the most frequently reported adverse experiences across all treatment groups was analyzed by a chi square test. The difference between each active medication group and the placebo group with respect to the proportion of subjects with laboratory abnormalities was analyzed by using a chi square test. Changes from baseline to the

follow-up visit for each laboratory test were also analyzed by the same two-way ANOVA used for the efficacy variables. Treatment groups were compared for mean changes from baseline in vital signs and body weights with two-way ANOVA.

RESULTS

Subjects and study conditions

Two hundred eighty-seven volunteers were screened for study participation, and a total of 264 subjects were randomized to double-blind treatment (Table II), which included 118 subjects at the San Diego site and 146 subjects at the Iowa City site. Five subjects were considered noncompleters after randomization to double-blind treatment, two for administrative reasons and three because of concurrent illness.

Randomized subjects ranged from 12 to 58 years old (mean age, 26.7 years); 128 were male and 136 were female. Weights ranged from 77 to 305 pounds (mean = 154.6 pounds). The five treatment groups were similar in demographics (Table II).

During each of the 2 study weekends, pollen counts, temperatures, and humidity were typical for the fall allergen season at each site.

Efficacy

As Table II demonstrates, there were no statistically significant differences between group means for either TSC or MSC at baseline (F test, $p > 0.924$). Further, there were no significant center-by-treatment interactions (F test, $p > 0.994$) for either TSC or MSC at baseline.

As shown in Fig. 1 and Table III, overall and across all 4 evaluation periods, the groups receiving 2 sprays of azelastine once daily (group 2) and 2 sprays of azelastine twice daily (group

TABLE III. Absolute and percent improvements in TSC scores by treatment groups and evaluation periods

Group	Absolute improvement (% improvement)					
	Period 1 (n = 264)	Period 2 (n = 261)	Period 3 (n = 260)	Period 4 (n = 260)	Overall (n = 264)	End point (n = 264)
1 – Azelastine 1 every 12 hours	6.59 (38.0)	4.20 (28.0)	3.18 (18.0)	6.69 (42.7)	5.15 (31.9)	6.60 (42.5)
2 – Azelastine 2 daily	6.39 (35.4)	7.37* (42.0*)	5.67 (27.8*)	9.80* (56.5*)	7.22* (40.0*)	9.65* (55.7*)
3 – Azelastine 2 every 12 hours	6.52 (39.6*)	5.15 (36.4*)	4.21 (24.6*)	7.27 (49.1*)	6.03 (37.9*)	7.56 (49.6*)
4 – Chlorpheniramine	6.62 (37.6)	6.20 (40.6*)	5.47 (29.9*)	8.81* (52.8*)	6.77 (40.2*)	8.81* (52.8*)
5 – Placebo	5.56 (26.2)	4.12 (13.4)	3.38 (6.9)	5.12 (24.4)	4.64 (18.5)	5.23 (25.2)

*Improvement in group from baseline was statistically significantly greater ($p \leq 0.05$) than the improvement in the placebo group from baseline.

TABLE IV. Improvement in individual symptoms in period 4 as compared with baseline

Group	Symptom						
	Nose blows	Sneezes	Itchy nose	Runny nose	Sniffles	Postnasal drip	Nasal stiffness
1 – Azelastine 1 every 12 hours	0.61	0.97	0.71	0.63	0.82	0.58	0.54
2 – Azelastine 2 daily	1.29*	1.02*	1.16*	1.11*	1.34*	0.97*	0.72
3 – Azelastine 2 every 12 hours	0.74	0.74	0.86*	0.77	1.02	0.56	0.50
4 – Chlorpheniramine	1.17	1.14*	0.94*	0.84	1.09*	0.74	0.54
5 – Placebo	0.48	0.33	0.40	0.58	0.68	0.51	0.50

*Improvement since baseline was statistically significantly greater ($p < 0.05$) than the improvement in the placebo group since baseline.

3) achieved clinically and statistically significantly more mean percent improvement (40% and 37.9%, respectively) in TSC than did the placebo group (18.5%). In contrast, the mean percent improvement in the group that received 1 spray of azelastine twice daily (group 1, 31.9%) was neither clinically nor statistically significant versus placebo. The mean percent improvement in TSC for the chlorpheniramine group (group 4) was statistically significant versus placebo overall.

After the initial dose of azelastine spray, the groups that received 2 sprays once daily and twice daily (groups 2 and 3) had similar mean percent improvements in period 1 of 35.4% and 39.6%, respectively, which exceeded the improvement seen in the placebo group (26.2%) and which was statistically significant versus placebo for the group receiving 2 sprays of azelastine twice daily (group 3, $p = 0.047$). During periods 2, 3, and 4, the

groups receiving 2 sprays of azelastine once daily and twice daily continued to experience persistent clinically and statistically significant mean percent improvement in the TSC as compared with the placebo group (Fig. 1 and Table III).

Similarly, Fig. 2 shows the mean percent improvements in MSC severity scores at each hourly evaluation time. Fig. 2 demonstrates again that at each evaluation hour the patients in the treated groups had more symptom improvement than did the patients in the placebo group, beginning 1 hour after treatment.

Additionally, as with the TSC severity scores, the azelastine groups had mean percent improvements in MSC severity scores across all 4 evaluation periods, ranging from 25.7% (group 1, 1 spray twice daily) to 43.6% (group 2, 2 sprays daily), which were clinically superior to placebo (11.5%). However, the mean percent improvements were statistically significant versus placebo only for the groups

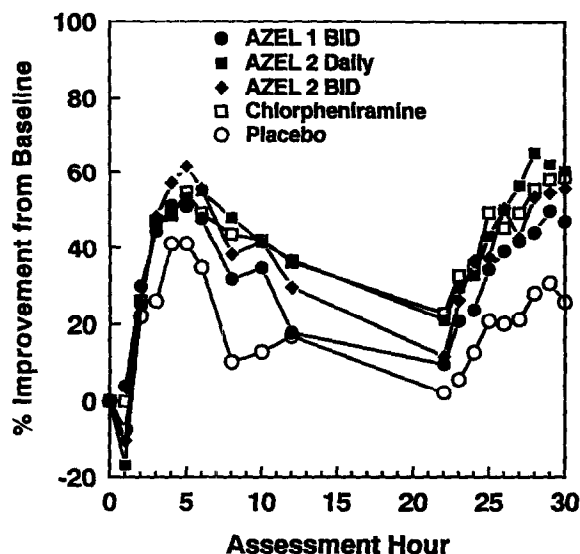


FIG. 1. TSC scores at each hour after treatment.

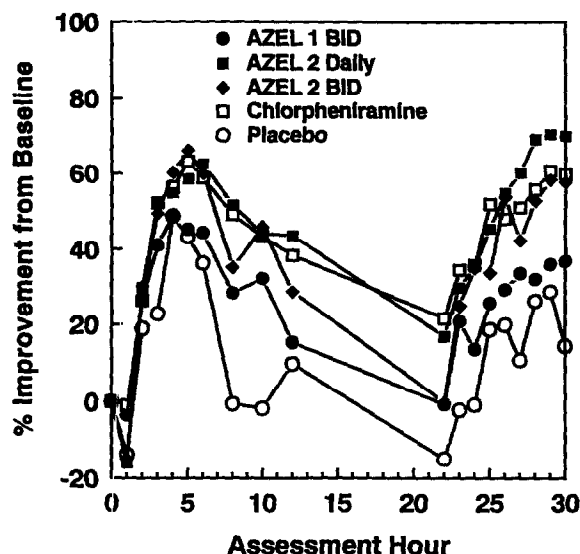


FIG. 2. MSC scores at each hour after treatment.

TABLE V. Percent improvement from baseline in TSC and MSC after the initial dose of medication for groups 2 and 3 combined compared with placebo

Hour	TSC		MSC	
	Azelastine	Placebo	Azelastine	Placebo
1	-13.5	-7.4	-15.4	-13.7
2	25.4	22.1	29.8	18.9
3	47.4*	26.0	50.7*	22.7
4	53.0	41.1	57.6	48.7
5	57.4*	41.0	62.3*	43.3
6	55.2*	34.7	61.2*	36.2
8	43.1*	10.3	43.4*	-0.6
10	41.5*	12.9	44.9*	-1.8
12	33.1	17.0	36.0*	9.7

*Improvement since baseline was statistically significantly greater ($p < 0.05$) than the improvement in the placebo group since baseline.

receiving 2 sprays of azelastine once daily and twice daily (groups 2 and 3, $p = 0.002$ and $p = 0.014$, respectively). The chlorpheniramine group (group 4) again had statistically significantly more improvement than the placebo group in all periods.

When individual symptoms were examined, in general, the mean improvements in all active treatment groups were superior to that for placebo. Table IV presents these data for period 4. The most statistically significant improvements in symptoms as compared with placebo were for the group receiving 2 sprays of azelastine daily (group 2). When stuffiness and TSC scores were added, the mean percent improvements for the group receiving 2 sprays of azelastine once daily (group 2) continued to be statistically significantly differ-

ent versus placebo in periods 2, 3, and 4 and overall ($p \leq 0.034$); the group receiving 2 sprays of azelastine twice daily (group 3) was also statistically significantly improved versus placebo in periods 2 and 4 and overall ($p \leq 0.024$). However, stuffiness was not statistically or clinically significantly improved in the treated groups compared with the placebo group.

The onset of action of azelastine nasal spray was examined further. The groups receiving 2 sprays of azelastine (groups 2 and 3) were combined and compared at each hour after the first dose of medication with the placebo group (Table V). The two azelastine-treated groups had a greater percent improvement in symptoms than the placebo group by the second hour, and this

TABLE VI. Subject global evaluations

Group	Improved		No change		Worse		p Value (vs placebo)
	No.	%*	No.	%	No.	%	
1 – Azelastine 1 every 12 hours	40	75	10	19	3	6	0.023
2 – Azelastine 2 daily	47	89	5	9	1	2	<0.001
3 – Azelastine 2 every 12 hours	45	83	8	15	1	2	<0.001
4 – Chlorpheniramine	40	77	10	19	2	4	0.009
5 – Placebo	24	49	22	45	3	6	–

*Percent of group.

TABLE VII. Number and percent of subjects who reported treatment-emergent adverse reactions

Group	Adverse event											
	Bad taste		Altered taste		Somnolence		Pharyngitis		Dry mouth		Headache	
	No.	%*	No.	%	No.	%	No.	%	No.	%	No.	%
1 – Azelastine 1 every 12 hours	3	6	2	4	3	6	1	2	3	6	16	30
2 – Azelastine 2 daily	4	7	1	2	6	11	5	9	1	2	16	30
3 – Azelastine 2 every 12 hours	5	9	4	7	5	9	2	4	1	2	19	35
4 – Chlorpheniramine	0		0		10	19	4	8	1	2	8	15
5 – Placebo	0		0		3	6	0		0		8	16

*Percent of group.

difference was statistically significant by the third hour.

Global evaluation

As shown in Table VI, subjects in all azelastine groups, as well as in the chlorpheniramine group, rated themselves as improved ($p \leq 0.023$) when compared with those in the placebo group.

Adverse events

No subjects in this study discontinued double-blind treatment because of clinical or laboratory adverse experiences; three subjects discontinued because of concurrent illness. The incidence of laboratory abnormalities after treatment was generally similar across all treatment groups, and none of the laboratory abnormalities was considered to be clinically meaningful.

The two adverse experiences that were probably related to the study drug and that occurred with greatest frequency in the azelastine treatment groups were taste perversion (19 subjects) and somnolence (Table VII). The frequency of taste perversion in the group that received 1 spray

of azelastine twice daily was 5 of 54 (9.3%). In the group that received 2 sprays of azelastine once daily frequency was 5 of 54 (9.3%), and in the group that received 2 sprays of azelastine twice daily, it was 9 of 54 (16.7%), which suggests a possible dose-dependent relationship. Twelve of the 19 subjects who reported taste perversion described a bad taste probably caused by the medication itself, and the other seven reported an adverse event compatible with distorted or altered taste perception. No taste perversion was reported in the chlorpheniramine or placebo groups, but somnolence was reported in these two treatment groups (19% and 6%, respectively). None of the headaches in the azelastine-treated patients was considered by the investigator to be probably or definitely related to the study medication.

All adverse experiences reported during the study were mild and resolved spontaneously without sequelae. The occurrence of treatment-emergent laboratory abnormalities was similar across all treatment groups. There were also no clinically significant changes in vital signs, laboratory pa-

rameters, or body weights from baseline screening to follow-up.

DISCUSSION

This study was designed to compare three doses of azelastine nasal spray and orally administered sustained-release chlorpheniramine maleate with placebo for efficacy, onset and duration of action, and safety. The design used for this study provided an ideal opportunity to evaluate drug efficacy in a rigidly controlled environment in subjects who have seasonal allergic rhinitis. Subjects at each site were exposed to the same environmental conditions (pollen counts, temperature, and humidity) and were closely supervised while in the park; they remained outdoors for the entire 8 hours on Saturday and Sunday to achieve maximal allergen exposure. This ensured that medication compliance was 100% and that 100% of the diary cards were completed on time and with all entries within range. Furthermore, only five of the 264 subjects who qualified in the park failed to complete the study.

There were no significant demographic or symptom score differences among the groups at baseline (Table II). The mean percent improvements in TSC and MSC severity scores for all three azelastine-treated groups exceeded the improvement that was seen with placebo at all hours and time periods, beginning at 2 hours after the initial dose of medication was given, as shown in Figs. 1 and 2 and in Table III. When these data were examined for statistical significance, it was clear that the groups that received 2 sprays of azelastine once daily and twice daily (groups 2 and 3) had statistically significantly more percent improvement in TSC and MSC scores at all periods after the first period, as well as at end point and overall, than observed in the placebo group (group 5). This was also observed when the data from groups 2 and 3 were combined and compared with placebo (Table V); the groups that received 2 sprays of azelastine had significantly more percent improvement in symptoms than did the placebo group with significant differences at hours 3, 5, 6, 8, and 10 for the TSC and MSC scores and at hour 12 for the MSC score. Although the group that received 1 spray of azelastine twice daily (group 1) exhibited some clinical activity, this treatment group failed to exhibit statistically significantly more mean percent improvements than the placebo group (group 5) in any period, overall, or at end point in either of the primary efficacy variables, TSC, or MSC severity scores. The chlorpheniramine group also had sta-

tistically significantly more percent improvement in TSC and MSC scores in all periods, at end point, and overall than the placebo group, which was consistent with its labeling as a medication that may be taken twice daily.

When individual symptoms in period 4 were examined (Table IV), again the subjects who received 2 sprays of azelastine twice daily (group 3) had the most improvement of the azelastine-treated groups and were comparable to the chlorpheniramine group (group 4). It is important to note that the chlorpheniramine and placebo groups (groups 4 and 5) received saline spray in place of the azelastine spray, which may have had an efficacy in these patients.

The duration of action of the azelastine nasal spray was examined, and the following observations suggest a duration of action of at least 12 to 24 hours.

1. Beginning 2 hours after the first dose of study medication, the mean percent improvement in TSC and MSC (Figs. 1 and 2) for the group that received 2 sprays of azelastine twice daily (group 3) exceeded the improvement in the placebo group (group 5), and this difference was seen throughout the remainder of this 12-hour dosing interval.
2. After the second dose of medication, TSC scores at hours 23 and 24 were improved over baseline by 26.2% and 36.6%, respectively, in the group that received 2 sprays of azelastine twice daily (group 3) versus 5.7% and 12.7% improvement from baseline, respectively, at hours 23 and 24 in the placebo group (group 5).
3. The group that received 2 sprays of azelastine once daily (group 2) had mean improvements in TSC and MSC (Figs. 1 and 2) for the first 12 hours after the initial dose of medication that were similar to improvements observed in group 3 and were statistically significantly greater than in the placebo group at 3, 6, 8, and 10 hours for the TSC and at 3, 6, 8, 10, and 12 hours for the MSC.
4. As shown in Table V, the mean improvements for groups 2 and 3 combined were 33.1% and 36% for the TSC and MSC, respectively, 12 hours after the initial dose of medication, compared with 17.0% and 9.7%, respectively, after placebo administration.
5. Finally, there is some evidence that azelastine was still active as long as 24 hours after administration. The mean percent improvement in the TSC scores for the group that received 2 sprays of azelastine once daily (group 2) was statisti-

cally significantly greater than that for the placebo group when hours 23 and 24 were examined individually ($p \leq 0.024$; data not shown) or when period 3 was studied (Table III).

The adverse experiences profile for azelastine demonstrated some taste perversion and somnolence. On further evaluation, the majority of the subjects who reported taste perversion described it as a bad taste that was probably due to the medication itself, and not to an alteration in taste perception. There did not appear to be a dose-response relationship to somnolence (Table VII). Overall, there were no clinically relevant changes in vital signs, body weight, or laboratory test results during azelastine therapy.

Azelastine has multiple activities and should be classified as a nonsteroidal antiinflammatory respiratory drug, as an antiallergic and antiinflammatory agent, rather than simply as an antihistamine. Indeed, orally administered azelastine has demonstrated clinical activity in the treatment of asthma³⁻⁵ and allergic rhinitis.^{1,2} Azelastine may be the first nonsteroidal oral medication approved in the United States to treat both upper and lower airway disease. This study also demonstrates that topical azelastine has activity in treating disease of the upper airways.

In this study, 2 sprays of azelastine once and twice daily were active in the treatment of allergic rhinitis in an acute setting without serious adverse effects. Although 1 spray of azelastine twice daily exhibited some antirhinitic activity, the group that received this dose of medication did not have statistically significantly more improvement than that observed in the placebo group. This study also demonstrated that 2 sprays of azelastine nasal spray had an onset of action within 2 to 3 hours with a 12 to 24-hour duration of action. This will serve as the basis for future studies to examine azelastine nasal spray in the long-term treatment of allergic rhinitis.

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